REMARKS

Upon cancellation of claims 27 and 30-32, claims 1-21 and 23-26 are pending in this application. Claims 1 and 12 are the only pending independent claims.

Claim 1 is directed to a method for functionally connecting portions of certain types of vertebrate nervous systems using a certain fibrin glue mixture comprising a growth factor, fibrinogen, aprotinin and divalent calcium ions (hereinafter the "fibrin glue mixture"). The method comprises bringing close to each other a portion of the peripheral nervous system and a portion of either the central nervous system or the peripheral nervous system, applying to the gap between the two portions the fibrin glue mixture, and suturing or anastomosing the two portions to be connected.

Claim 12 is directed to a method for functionally reconnecting an avulsed cervical root (a portion of the peripheral nervous system) to the spinal cord (a portion of the central nervous system) of a vertebrate using the fibrin glue mixture, by bringing the avulsed cervical root close to the spinal cord, applying the fibrin glue mixture to the gap between them, and forming an attachment between them.

Thus, in general, both of the independent claims are directed to connecting or reconnecting nerves or the like of the peripheral nervous system to the spinal cord or another portion of the central nervous system or to another peripheral nerve or other portion of the peripheral nervous system. The method claims are not directed to connecting together different portions of the central nervous system to each other. This is an important distinction.

Claims 1-21 and 23-27 were rejected under 35 U.S.C. § 103(a) on the grounds of obviousness over Cheng et al. U.S. Patent 6,235,041 (hereinafter "Cheng et al.") in view of Schenck et al. U.S. Patent 4,553,542 (hereinafter "Schneck").

The Examiner, in essence, took the position that Cheng et al.. discloses all that is claimed in claim 1 except for suturing or anastomosing the portions of the claimed nervous systems to connect them, and that Schneck discloses such suturing or anastomosing. Regarding claim 12, the Examiner, in essence, took the position that the combination of Cheng et al. and Schneck discloses connecting any portion of the nervous system of a vertebrate including the cervical root to the spinal cord. In view of these asserted disclosures, the Examiner concluded that independent claims 1 and 12, and their dependent claims would have been obvious at the time of

the invention to a person of ordinary skill in the art. Applicant respectfully, but strongly disagrees.

The Examiner is respectfully directed to Dr. Cheng's Declaration, accompanying this Amendment. As noted in paragraph 1, and amply supported by his impressive curriculum vitae attached to Dr. Cheng's Declaration as Schedule 1, Dr. Cheng, the sole named inventor in the present application, is truly an expert in the field of repair of spinal cord and nerve roots (which includes cervical roots and are also called spinal roots) after trauma and neural regeneration and trophic factor. Part of his research led to the present invention, directed to new method of functionally connecting a portion of the peripheral nervous system to a portion of the central or peripheral nervous system of a vertebrate by applying to the gap the claimed fibrin glue mixture (Dr. Cheng Declaration, paragraph 2). Using the method of the invention in laboratory rats has resulted in demonstrated remarkable return of function to the animals, namely free motion of an affected elbow, ability to fully extend claws and ability to bear weight, after peripheral nerves, represented by cervical nerves, were severed from the spinal cord, which is a portion of the central nervous system, compared to control rats which were subjected to the same nerve severance, but using a fibrin glue that lacked the growth factor of the fibrin glue mixture of the present invention. These results are shown at least in Example 1 of the application, where such results are summarized in paragraph 3 of Dr. Cheng's Declaration.

In paragraph 4 of Dr. Cheng's Declaration, the results are summarized of treatment of laboratory rats with transected peripheral nerves, namely sciatic nerves, using the fibrin glue mixture in the method of the present invention having a growth factor, compared to control rats using a fibrin glue without a growth factor, as detailed in Example 4 of the present application. Eight weeks postoperatively, the lesion degree was evaluated by the Sciatic Function Index (SFI), explained in more detail in the application, and the rats receiving the repair method of the present invention had higher scores, which means a better recovery.

Thus, the application demonstrates, and Dr. Cheng's Declaration reinforces, that the method of the invention is quite effective in repairing the indicated nerve structures involving connection or reconnection of the peripheral nerves with the spinal cord (a central nervous system structure) or other portions of the peripheral nerves. As noted above it is important for the present invention that the method is used on peripheral-central or peripheral-peripheral

connections, rather than central-central connections. Dr. Cheng's Declaration explains this importance with reference to the cited references to refute the conclusion of obviousness.

Please note that the inventor of the present invention, Dr. Henrich Cheng, is the same Dr. Henrich Cheng who is the primary or first-named inventor in Cheng et al. (Dr. Cheng's Declaration, paragraph 5). Thus, better than anyone, Dr. Cheng can draw a sharp distinction between the present invention and the subject matter of Cheng et al.. Cheng et al. is directed to a medical device of a biocompatible material for use in the treatment for a gap or defects in the central nervous system, that is adapted to enable connection of nerve fibers of gray and white matter between the proximal end and distal end thereof in predetermined openings (see Abstract). However, the present invention (the '530 application in Dr. Cheng's Declaration, *Id.*) provides a method of functionally connecting a portion of the peripheral nervous system to a portion of the central or peripheral nervous system. A clear diagram, Fig. 1 in Dr. Cheng's Declaration, shows the exact positions for connection in Cheng et al. and the present application, respectively, which should be helpful to clarify the difference between the two cases. The repairs of the different types or regions of the nervous systems involved different mechanisms. Therefore, there was no way for Dr. Cheng, let alone a person of ordinary skill in the art, to have been able, at the time of the invention, to anticipate the effect in connecting a portion of the peripheral nervous system to a portion of the central or peripheral nervous system in view of Cheng et al.

Dr. Cheng's Declaration, paragraph 6, explains in detail the different structures and functions of the central nervous system on the one hand and the peripheral nervous system on the other hand, and why they are meaningfully different in the context of the present invention, especially compared to Cheng et al. The central nervous system is made up of the spinal cord and brain, both of which contain "white matter" and "gray matter." White matter is bundles of axons coated with a sheath of myelin, and gray matter is masses of cell bodies and dendrites. Thus, in the central nervous system, each pair of spinal cord nerves is "mixed" nerves, containing sensory and motor axons. However, peripheral nerves are not "mixed" nerves. Neither the sensory nor the motor nerves of the peripheral nervous system contains "white matter" and "gray matter." Cheng et al. only dealt with the connection of a break of the spinal cord. More particularly, Cheng et al. provides a device and method for connecting the "gray matter" and "white matter" in the spinal cord. The present application claims a method for

connecting the spinal cord and a peripheral nerve (i.e., nerve root, for example) or for repairing the gap or defect in a peripheral nerve with the fibrin glue mixture as claimed, that contains a growth factor, such as in one preferred embodiment, an acidic fibroblast growth factor (aFGF), and it has nothing to do with white matter and gray matter. Because of the different structure and function between the spinal cord or the central nerves on the one hand, and the peripheral nerves on the other hand, there was no way to expect either the medical device or the fibrin glue composition of Cheng et al. to work on the peripheral nervous system. Careful and meaningful experimentation was necessary to invent the subject matter claimed in the present application. Given the above, the present invention was not and would not have been obvious over Cheng et al.

Thus, Cheng et al. did not as a practical matter disclose everything claimed in claim 1 or 12, except the sutures or anastomoses or the ultimate connection or reconnection of a portion of the peripheral nervous system to either a portion of the central nervous system or another portion of the peripheral nervous system as claimed in the present application. The deficiencies of Cheng et al. are not overcome by Schenck.

As explained in paragraph 7 of Dr. Cheng's Declaration, Schenck taught an anasotmosis device and method for using it to join a tubular anatomical structure that is supported with the body by connective tissue and has a prepared open end to a second anatomical structure, such as blood vessels, fallopian tubes, ureters, vas deferens and outer nerve sheaths (see abstract and claim 1). The use of Schenck's encircling anastomosis device would not be useful for, and therefore is totally irrelevant to a method for connection between nerves, which are not hollow tubes. What might work for connecting nerve sheathes may not be effective in connecting nerves. Moreover, Cheng et al. and Schenck, are properly combinable, because of the different structure and functions of nerves involved in Cheng et al., compared to the anatomical structures repaired in Schenck. Even assuming only for the sake of argument that these references are properly combinable, as refuted above, the combination does not teach or suggest the presently claimed invention.

Schenck neither describes nor provides a definition of "nerves" and therefore, does not recognize any difference between the central nervous system nerves and the peripheral nervous system nerves. Further, Schenck does not provide any examples showing any success in the recovery in function after using the anastomosis device. As mentioned above, "nerves" in

different regions, central vs. peripheral, have different functions and structures. Schenck neither taught nor suggested the connection between the spinal cord and a peripheral nerve (i.e., nerve root, for example) or the connection of a break of a peripheral nerve with the fibrin glue mixtures containing a growth factor of the present invention, such as aFGF. Even though the nerve sheaths were anastomosed by the device of Schenck, there was still no evidence to show that such nerve sheath repair resulted in any functional recovery.

Additionally, one skilled in the art would not have even suggested or thought about the effect of the fibrin glue mixture comprising a growth factor as claimed in connecting a portion of the peripheral nervous system to a portion of the central or peripheral nervous system, in view of either or both of Cheng et al. and Schenck. A person skilled in the art would not have had any motivation based on either Cheng et al. or Schenck, even if combined, to use the fibrin glue mixture of the present invention to connect a portion of the peripheral nervous system to a portion of the central or peripheral nervous system.

Because of the different anatomical body components being treated by Cheng et al. and by Schenck, and even further, the significant distinctions between the present invention and the references, even as combined, as explained in Dr. Cheng's Declaration, the present invention as claimed in independent claims 1 and 12 would not have been obvious over Cheng et al. in view of Schenck.

Claims 2-11 and 23-24 are dependent claims that ultimately depend from independent claim 1, and therefore, they should be patentable for at least the same reasons as set forth above concerning the patentability of claim 1.

Independent claim 12 is more specific than claim 1, and recites a method of functionally reconnecting an avulsed cervical root (that is a portion of the peripheral nervous system) to the spinal cord (a portion of the central nervous system) using the fibrin glue mixture as claimed. Since this claim is more specific than claim 1 regarding the connection of a particular type of nerve from the peripheral nervous system to the spinal cord, claim 12 also would not have been obvious to a person of ordinary skill over the cited references, even when combined.

Claims 13-19 and 25-26 ultimately depend from independent claim 12, and therefore, these claims should be patentable at least for the same reasons that claim 12 is patentable.

Respectfully submitted,

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